Smoking Cessation, Varenicline, and Suicide: A Systematic Review

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Abstract

**Background:** Varenicline was approved for use in the United States in 2006, and has proven to be the most effective smoking cessation therapy currently available. Unfortunately, there have been some recent concerns regarding its safety. The FDA added a black box warning to varenicline in July, 2009, advising patients and providers of the possible link between varenicline and suicidal ideation and/or behaviors. The addition of the black box warning to varenicline has lead to several studies to investigate whether or not there is a causal relationship.

**Method:** An exhaustive search of the available medical literature was performed using MEDLINE, Web of Science, PubMed, CINAHL, Evidence-Based Medicine Reviews Multifile, PsycINFO, and International Pharmaceutical Abstracts, using the keywords “varenicline”, “suicide”, and “depression”.

**Results:** Four studies were identified and included in this review, including one randomized control trial, two observational cohorts, and one open-label trial. In the RCT, there were no cases of suicidal behaviors, and a minimal increase in depressed mood and mood disturbances when compared to placebo. One cohort showed a minimal risk increase of fatal and non-fatal self harm when compared to nicotine replacement therapy (NRT), and an increased risk of suicidal ideation. In the second cohort, there were four cases of attempted suicide and two cases of suicidal ideations. One percent of the study group reported depressed mood, and less than one percent reported mood change. The open-label trial reported no increase in scores related to suicidality, and a reduction in mood changes and depression.

**Conclusion:** This review used the GRADE analysis for each study, and the outcomes analyzed were depression, suicidal ideations/behaviors, and fatal and non-fatal self harm. The overall GRADE of the evidence was very low. But varenicline has still proven to be the most effective form of smoking cessation available to date. And while there may be a minimal increased risk of suicide with its usage, the risk of eventually dying from smoking related illness for smokers is 50%. There needs to be further studies conducted on patients who are at an increased risk of suicide, mainly those with depression and/or other psychiatric illnesses, to see if the use of the drug is safe in these populations. Providers should continue to prescribe its use in these populations with caution. But for the general public, it appears to be a safe and effective means of smoking cessation.

**Keywords:** Varenicline, suicide, suicidal ideation, suicidal behaviors, depression

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Biography

While technically Heather was raised and lived in Virginia for most of her life, she denies her true southern roots, claiming she is in fact a Pacific Northwesterner. She attended both high school and college in VA, graduating with a bachelor’s in Business Administration. After a short stent working as a financial analyst in Washington DC, she moved to Seattle to give the other coast a whirl. After working as a budget analyst at a public health organization, she decided she would be better suited in another career. She enjoyed the medical side of her organization, so she decided to become an EMT to get further exposure and experience. She was introduced to the role of the physician assistant through her job, and decided to apply to the PA program at Pacific University, which she began in the summer of 2009. After graduation, Heather plans to move back to Seattle, get married, adopt a dog, and live happily ever after.

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INTRODUCTION

Background

Cigarette smoking continues to be a world-wide health problem, and is the leading preventable cause of death in the U.S., causing approximately 443,000 deaths in the U.S. annually (Centers for Disease Control and Prevention, 2008). Approximately 50% of smokers will eventually die from a tobacco related cause, including, but not limited to, coronary artery disease, cancer, chronic obstructive pulmonary disease, stroke, peripheral vascular disease, and aortic aneurysms.

Smoking cessation programs, therapies, and preventions continue to be designed and evaluated by both government and private agencies due to the numerous smoking related health issues.

Varenicline, the newest smoking cessation therapy, was introduced by Pfizer and approved by the Food and Drug Administration (FDA) for use in the United States in 2006. It is the third product approved by the FDA for smoking cessation, the other two being nicotine replacement therapy (NRT) and bupropion (Cahill, Stead, & Lancaster, 2009). Varenicline’s mechanism of action differs from both NRT and bupropion, acting as a partial agonist of the alpha4beta2 acetylcholine receptors in the brain and nervous system, which causes a subsequent release of dopamine (Jiménez-Ruiz, Berlin, & Hering, 2009). This replicates the effect that nicotine has on the brain. It is thought that varenicline assists in smoking cessation by decreasing the symptoms of tobacco withdrawal, which include irritability, mood changes, anxiety, insomnia, restlessness and weight gain. Additionally, varenicline has an affinity for the
alpha4beta2 receptors that is 15 times stronger than that of nicotine (Kasliwal, Wilton, & Shakir, 2009), therefore, when a patient smokes a cigarette while taking varenicline, the effect of nicotine on the brain is limited, hence reducing the “reward” sensation that people experience while smoking.

Varenicline has proven to be the most effective smoking cessation therapy thus far (Jiménez-Ruiz et al., 2009). According to Cahill (2009), when compared to use of a placebo, smokers more than doubled their chances of remaining abstinent at the six month mark following initial therapy. When compared to NRT and bupropion, users of varenicline had approximately a 30% and 50% greater chance of success of continued abstinence at the six month mark, respectively (Cahill et al., 2009). With such improvement in cessation rates, it is not surprising that varenicline is estimated to have been prescribed to approximately 3.5 million people in the United States (Moore, Cohen, & Furberg, 2008).

While the smoking cessation rates among users are impressive, there have been some recent concerns regarding the safety of varenicline. The FDA provides the general public and medical personnel an avenue for reporting adverse drug events and reactions on a voluntary basis, known as the Adverse Event Reporting System (AERS). By November 27, 2007, 153 cases of suicidal adverse events had been reported via the AERS (U.S. Food and Drug Administration, 2009). These events included 116 cases of suicidal ideation, and 37 cases of suicide. Because of the possible correlation of varenicline and suicide, the FDA published a formal Public Health Advisory in February, 2008 (Moore et al., 2008). The FDA then added a black box warning to varenicline in
July, 2009, advising patients and providers of the possible link between varenicline and suicidal ideation and/or behaviors (U.S Department of Health & Human Services, 2009). The addition of the black box warning to varenicline has lead to several studies to investigate whether or not there is a causal relationship. It has been observed that smokers have a 2-4 times greater risk of suicide compared to non-smokers, based on addictive personality types (Miller, 2000). And due to withdrawal symptoms, which include depressed mood, it is difficult to make a direct causal relationship between the use of varenicline and suicidal events. These health and safety concerns have lead to this relationship being evaluated in several studies.

Purpose of the Study

The use of varenicline for smoking cessation has been associated with a possible increased risk for suicidal ideations and behaviors in recent years. The purpose of this systematic review is to examine the correlation between the use of varenicline and this risk of suicide, and to determine if the risks of suicidal adverse events outweigh the benefit of smoking cessation. The outcomes will be evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE), which is method used to determine the quality of the evidence (see Table 1) (Guyatt et al., 2008).

METHOD

An extensive literature search was performed using MEDLINE, Web of Science, PubMed, CINAHL, Evidence-Based Medicine Reviews Multifile, PsycINFO, and International Pharmaceutical Abstracts. All databases were
accessed through the Pacific University Library system. A search was performed using the keyword “Varenicline” in each database, resulting in a total of 1,888 articles. The keyword “suicide” was then combined with “Varenicline”, which resulted in 71 articles. Another search was performed combining the terms “Varenicline” and “depression”, which yielded an additional 114 articles. There was significant overlap between articles retrieved from the multiple databases. Articles were then limited to the English language and human subjects. Traditional reviews and individual case studies were excluded from the results. The remaining 15 articles were reviewed for content and included if they contained information on suicide, suicidal ideation, or suicidal behaviors as a primary outcome. Four articles met the above stated criteria, and were included in this systematic review.

RESULTS

A total of four studies were included for review based on the content, on the study design, and on the use of suicidal ideation or behaviors as a measured outcome. One randomized control trial, two cohort studies, and one open-label trial were reviewed.

Rigotti et al.

In 2010, Rigotti et al. performed a randomized, double blinded control trial to determine whether using varenicline in patients with stable cardiovascular disease (CVD) was a safe and effective means smoking cessation. The trial enrolled 714 current smokers, all of whom had stable CVD for at least two months, and all of whom had not attempted to stop smoking within the past three
months. The participants enrolled were between 35 and 75 years old, were predominantly male, and were from various locations (15 countries were included). Excluded were patients with a diagnosis of depression, a “history of psychosis, panic disorder, or bipolar disorder”, or those who had received antidepressant medications within the last year. The participants were randomly assigned to receive the placebo or varenicline for 12 weeks. The study participants were divided into two groups; 353 participants received varenicline and 350 participants received a placebo, and both groups received smoking cessation counseling.

While the primary outcomes of the study measured continued abstinence rates (CAR) and cardiovascular events, because of the recent concern regarding a correlation between varenicline and suicide, the study also measured “treatment-emergent adverse events”, which looked at suicidal behaviors and depressed mood, along with other adverse events (AE) (Rigotti et al., 2010, p. 226).

The study found that 11 participants (3.1%) in the treatment group and 8 participants (2.3%) in the placebo group experienced a “depressed mood disorder or disturbance” either during treatment or within the 52 week follow up period. Additionally, 9 participants in the treatment group (2.5%) and 3 in the placebo (0.9%) experienced an “other mood disorder”, which includes dysphoria, mood alterations or swings, and/or an emotional disorder. Neither the treatment nor the placebo group had any reports of suicidal behaviors over the treatment and follow up period. The authors concluded that varenicline appears to be
safe for use in people with CVD. They also felt that while it did not cause an increased risk of psychiatric events in their study population, further studies should be conducted in order to make a definitive assessment of these risks.

Gunnell et. al.

A cohort study, performed in 2009 by Gunnell, D. et al., attempted to examine the association of suicide and varenicline by comparing smoking cessation pharmacotherapy (either varenicline or bupropion) with NRT. The study identified participants through the UK General Practice Research Database (GPRD). Eligible participants were 18 or older and prescribed a new course of varenicline, bupropion, or NRT between 9/1/2006-5/31/2008. The study identified 80,660 eligible participants, of whom 10,973 received varenicline, 6,422 received bupropion, and 63,265 received NRT. All participants were from general practices located throughout the United Kingdom. Participants were entered into the cohort on the date the prescription was written and followed through the treatment period, and then for an additional three months. Electronic medical records were obtained for participants during both the treatment and follow-up period.

Outcomes measured in this study included “fatal and non-fatal self harm, suicidal thoughts”, and depression, which was measured as being the initiation of an antidepressant therapy over the treatment or follow-up periods. Suicides were identified through the GPRD system via medical codes. Death certificates for the suicides were not obtained.
The characteristics of the exposure groups were similar, with a few notable exceptions. There was a higher percentage of people with previous mental health consultations in the NRT (4.1%) compared to the both the bupropion (2.4%) and varenicline (2.5%) groups. Also, alcohol misuse was slightly higher in the NRT compared to bupropion and varenicline (10.6% vs 7.3% vs 8.3%). Additionally, current use of antidepressants, hypnotics, and antipsychotics were all slightly higher in the NRT groups compared to the pharmacotherapy groups. The previous smoking cessation attempt rates were also slightly lower in the NRT group when compared to the other two. Males had a slightly higher incidence of receiving pharmacotherapy compared to NRT.

The baseline used for comparison of outcomes was NRT. Over the course of the study, there were two cases of fatal suicides, and both occurred in the NRT group. There were a total 166 cases of non-fatal self-harm incidences reported, with 9 in the bupropion group and 18 in the varenicline group. The hazards ratio for both varenicline and bupropion suggests a decreased rate of self harm, but when they were adjusted for possible confounding factors, there was a slightly increased risk. The confounding factors that appeared to have the greatest effect on the hazards ratio were past and current antidepressant usage. The adjusted hazards ratio for varenicline compared to NRT was 1.12 (with a confidence interval (CI) of 0.67-1.88). This suggests only a slightly elevated risk of 12% when using varenicline compared versus NRT. The hazards ratio for bupropion was similar at 1.17 (CI of 0.59-2.32).
There is an increased risk of suicidal thoughts with varenicline and bupropion use compared to NRT, with an adjusted hazards ratio of 1.43 (CI 0.53-3.85) and 1.20 (0.28-5.12). Therefore there is a 43% greater risk of suicidal thoughts with varenicline as compared to NRT.

Both the varenicline and bupropion groups were at a decreased risk of being started on a new antidepressant medication when compared to NRT. The adjusted hazards ratio for varenicline was 0.88 (CI of .77-1.00) and for bupropion was 0.91 (CI of 0.77-1.07). Therefore, the study concluded that the usage of varenicline is not associated any major risks for depression.

Kasliwai et al.

The second cohort study, conducted by Kasliwai R. et al. (2009), attempted to determine whether or not varenicline is associated with an increased suicide risk. In addition to the primary outcome, the authors also looked at adverse psychiatric events. There is no comparison or placebo used. The cohort study is not yet completed, and this article aimed to present the interim results of an ongoing study.

The study design was an observational cohort, but used a “modified prescription event monitoring methodology.” The Drug Safety Research Unit (DSRU) identified participants who were prescribed varenicline by a general practitioner (GP) after December 2006. Then a detailed questionnaire was mailed to the patient’s GP, approximately four months following the initial prescription. The questionnaire contained questions regarding the patient’s demographics, medical history, smoking history, dates of treatment, “clinical
event data (obtained during treatment and 1 month after stopping varenicline), and dosage. Patient’s names were excluded, and the patients were identified by a number. The GP was also asked to indicate if they suspected any adverse events related to the drug. The GP was asked to fill out the questionnaire, and return it.

Thus far, 2,682 studies have been processed and included. Studies that were not completely filled out were excluded. The participants were predominantly female (at 60.7%), middle aged, and smoked between 11 to 20 cigarettes daily. Over half the participants had previously attempted to quit.

According to the study, there were four cases of attempted suicide and two cases of suicidal ideation. Two of the suicide attempts took place while the patients were still taking the medication, and the other four events took place after treatment had stopped. None of the attempts were fatal. All four of the patients that attempted suicide had a history of depression, and one had a history of alcohol dependence. All four of the attempts also had some sort of precipitating stressor before the attempt. In the two cases of suicidal ideation, one of the patients had a history of depression. The other had an issue with recent life stress.

The questionnaire also addressed the issue of depression and other psychiatric events. According to the study, 29 patients (approximately 1.1% of the study) had disclosed depression as an adverse event. Additionally, 17 participants (0.6% of the study) reported a mood change or emotional
disturbance. The most reported psychiatric events were sleep disturbances and anxiety.

The authors of the study choose not to make any definitive conclusions, since the results of the study would continue to change as more and more responses are received. They felt that, in the meantime, caution should be used when prescribing varenicline to patients with any existing psychiatric illnesses.

Philip et al.

The fourth study included in this review was conducted by Philip, N. et al. (2009). The purpose of this open-label study was to determine whether treatment with varenicline in smokers with diagnosed depression, who were currently taking antidepressants with limited response, would decrease depressive symptoms. The total study period was eight weeks in duration. Participants of the study were identified through outpatient clinics at a psychiatric hospital. Eligibility criteria included an Axis I diagnosis via the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV-TR) of a “mood disorder with predominating depressive symptoms”, current antidepressant therapy for at least 6 weeks, “persisting depressive symptoms, defined as a Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR-16) score of greater than 5”, and nicotine dependence. Patients with renal dysfunction, or who are currently pregnant or breastfeeding were excluded. Additionally, patients with a varenicline intolerance were not enrolled. A total of 18 participants enrolled in the study, aged 18-65. Study participants were predominantly female (at 66.7%). The current mood medications prescribed were selective serotonin reuptake
inhibitors (44.4%), serotonin-norepinephrine reuptake inhibitors (11.1%), mood stabilizer (16.7%), and other antidepressants (27.8%). The average number of cigarettes smoked per day was 18.7, although the range was 10-80.

The primary outcome measured was a decrease in points via the QIDS-SR. Patients completed the QIDS-SR at baseline, and repeated it every two week at the clinic visit until the end of the follow up period at week eight. Additionally, both patients and providers were asked to fill out the Clinical Global Impression-Severity of Illness (CGI-S) and the CGI-Improvement (CGI-I) scales at each visit.

Fourteen of the original study participants completed the study, with four discontinuing the medication early due to adverse effects, including nausea and anxiety. The average decrease in the QIDS-SR score over the eight week study period was 4.7. Six of the patients achieved remission of their depressive symptoms (classified as a QIDS-SR of 5 of less), and eight had notable decrease in their scores. There was no significant change in the patient rated CGI-S score, but the provider rated score decreased on average from 3.1 (±/-.1.1) at baseline to 2.1 (±/-.1.4) at the study end.

While suicidal mood and behaviors were not addressed at the beginning of the study, “a post hoc analysis was performed to examine the changes on the specific core QIDS-SR-16 mood and suicide items”, which are listed as number 5 and number 12 on the QIDS-SR-16 survey (Philip, Carpenter, Tyrka, Whiteley, & Price, 2009). There was no increase in scores related to suicide, and a notable decrease in score related to mood changes, with a baseline score of 1.98 (±/-.
0.76) to a study end score of 1.22 (+/- 0.65). The authors concluded that varenicline appears to be effective for smokers with depression, but that more comprehensive, double-blinded studies would need to be performed to confirm these study results.

**DISCUSSION**

Smoking is a huge world-wide health burden, so effective cessation therapies will continue to be researched and developed. With the advent of varenicline, smokers have a new option for cessation therapy, which has proven to be more effective than placebo, bupropion, and NRT for long term cessation (Cahill, Stead, & Lancaster, 2008). When compared to placebo, the participants taking varenicline had more than twice the chance of successfully quitting at six months (Cahill et al., 2008). But, with the new safety concerns regarding suicidality and suicidal behaviors, providers may not be as willing to prescribe it as other forms of cessation therapy, regardless of its higher level of efficacy. Therefore, determining whether or not varenicline can be safely used in patients is an important issue.

The discussion regarding the possible correlation between varenicline and suicide is fairly new; therefore there are a limited number of studies that address the issue directly.

Rigotti et al.

In the study performed by Rigotti et al. (2010), the main focus was to determine whether varenicline could be used safely in patients with CVD, but it also addressed adverse events, including issues of suicide and depression. It
was the only randomized controlled trial included in this review. The limitations of the study included the exclusion of patients with a diagnosis of depression, and those who had taken any antidepressants within past year, which would tend to distort the results relevant to mental health issues. The methods for determining the adverse events that occurred to participants during the study were not disclosed within the article, which makes it difficult for the reader to have confidence in the results.

The authors did note, that in order make a definitive case that there is not a strong correlation between varenicline and suicide, a more “systematic assessment” of suicidal symptoms would need to be conducted (Rigotti et al., 2010, p. 227). There were no instances of suicidal behaviors within the 714 participants, and a minimally increased rate of depressed mood and mood disturbance.

The exclusion of participants with depression makes it difficult to determine whether varenicline can be used safely in this population, although according to the study, patients without depression or other psychiatric illness appear to be able to safely take the drug.

Gunnell et al.

The main purpose of the study conducted by Gunnell et al. (2009) was to determine whether there was an increased risk of suicidal behaviors and ideation. This was the largest study included in this review, and was the only study that used NRT as a comparison. The authors noted that the power of the study is limited, because when compared to the general population, the rate of
suicide for the entire cohort was lower than would have been expected. Additionally, death certificates were not obtained for all deaths over the study period. Therefore, it is possible that some instances of suicide were not included in the study.

Also noteworthy, is the fact that baseline characteristics of the NRT and varenicline group differ in several important areas. A larger percentage of the NRT had previously experienced mental health issues. Additionally, the NRT had a higher instance of alcohol misuse and previous mental health consultations. This could indicate a provider preference with use of NRT versus pharmacotherapy in these populations. More reliable statistics could have been obtained had the study findings been better balanced at baseline.

The study suggests a minimal increased risk of both fatal and non-fatal self harm when compared to NRT, but this risk is small, and because of a wide CI, the risk is imprecise. The authors say that while the CI is wide, the upper limits of the 95% CI approach 2, and therefore a twofold risk increase cannot be disregarded. This risk appears to be small and the risk of suicide with its use is minimal.

The risk of suicidal thoughts when taking varenicline was higher when compared to NRT, with a 1.43 hazards ratio, meaning there is a 43% greater risk of suicidal ideations on the medication. But again, this CI for this hazards ratio is wide, and imprecise. Also, there is no information regarding NRT and its associated risk of suicidal ideation. Therefore, because of the limited information
within the study, a 43% risk increase may be rather insignificant, if the risk of suicidal ideation with use is minimal.

The study also addressed the issue of depression. The study used the initiation of antidepressants during follow up in order to decide which participants had a new diagnosis of depression. The authors found a decreased risk of initiation of antidepressant therapy when compared to NRT. But this excludes any patients who may have experienced a new onset of depression who did not receive antidepressant therapy. As there are multiple other methods of treatment for depression, including counseling and behavior change therapy, the measurement of antidepressants therapy may exclude multiple new cases of depression.

There appears to be a small risk of suicidal ideation and behaviors when compared to NRT. Additionally, while there is a possibility of a twofold increased risk with varenicline, the general risk of suicide with its use appears to be low, when compared to the general population. This study cannot definitively state that there is not a risk of suicide with the use of varenicline, but this risk appears to be minimal.

Kasliwai et al.

The study by Kasliwai et al. (2009), looks at the use of varenicline and the risk of suicidal behaviors and ideations. With only four suicide attempts and two ideations (less than 1% of the total study), the correlation between suicide and varenicline appears again to be minimal. But, this study likewise has some limitations. This interim report reflects a small portion of the study that will
ultimately result. Thus, the authors were not yet able to assess the response rate, given that not all the questionnaires have been returned. Furthermore, as this is an ongoing study, the sample size will increase, and the results will likely change. The study included only varenicline prescribed by an actual GP, and not by other healthcare practitioners. Hence, a large portion of the population who are taking varenicline may have ignored. The study also fails to give any baseline characteristics of the population, so the reader is unable to determine what proportion of the cohort has other psychiatric illnesses or co-morbid conditions.

The study does use a standardized questionnaire for GPs to fill out based on patient reports. The questionnaire is detailed (per the authors), to give a broad picture of all the adverse events. But the overall power of the study is low, due to the questionable response rate of the providers.

Philip et al.

The aim of the study by Philip et al. (2009) was to determine whether or not use of varenicline as an adjunctive therapy to antidepressants, improves symptoms in patients with diagnosed depression. The study used the QIDS-SR-16 to assess changes in depression symptoms, mood changes, and suicidal ideation/behaviors. The study found no evidence of increased suicide ideation/behaviors based on the questionnaire. The study also reported a slight increase in mood score from baseline to study end. But, this study has several severe limitations, which make its findings less reliable. To begin with, the study design was open-label, and therefore bias could be easily introduced, as no
blinding or concealment occurred. Moreover, the study had only 18 participants, which limits its power based strictly on the small sample size. The study period was short, and there was no follow up after discontinuation of the medication. Furthermore, while the providers did not alter the other antidepressants that the patients were taking over the course of the study, they were able to prescribe both benzodiazepines for anxiety and trazodone for sleep issues, which could have affected the outcomes of the study. Additionally, the study used the QIDS-SR-16, which is depression score questionnaire, to determine depressive symptoms, mood changes, and suicidal ideation/behaviors. While the questionnaire is designed to determine depressive symptoms, there is only one question that addresses suicide head on. Due to the limited number of questions addressing this specific outcome, and because the suicide analysis was done after the study had been completed, this study is of limited value for determining whether there is a risk of suicide while taking varenicline.

Conclusions

Only two of the studies included in this review were to address the issues of varenicline and suicidal behaviors and ideation, but one of the two was not completed. The other two studies chose to address and analyze the issues of suicide only after the study had been completed, so those outcomes were not introduced until after the studies had been designed. Both the Gunnell et al. (2009) and the Rigotti et al. (2010) studies included comparisons (NRT and placebo), while the other two studies had no controls.
As mentioned earlier in this review, the GRADE method was used to review the quality of the evidence and outcomes within each study. The outcomes specifically addressed in this literature review were suicide attempts and/or behaviors, suicidal ideation, and depression.

The outcome for suicidal attempts and/or behaviors was included in three of studies, and two of the studies were downgraded. The study conducted by Kasliwal et al. (2009), had a starting GRADE of low evidence with no changes. The Gunnell et al. (2009) study, which also started at a low GRADE, was decreased to very low due to the lack of precision in regards to the confidence interval, since it was wide and crossed one. The study conducted by Rigotti et al. (2010) was also downgraded in several areas. The study started at a high GRADE because it was a RCT, but it was lowered one level within the study quality category due to the lack of disclosure on how suicidal attempts and/or behaviors were determined in the study participants. Furthermore, the study was downgraded again in the precision category due to the lack of suicidal events, which resulted in a low GRADE of evidence. Overall, combining the studies, the suicidal attempts and/or behaviors outcome received a low GRADE for the quality of the evidence.

The second outcome reviewed was suicidal ideation, which was also addressed within three of the studies. Again, the study conducted by Kasliwal et al. (2009), had a starting GRADE of low evidence with no changes. The Gunnell et al. (2009) study was given an initial a low GRADE and downgraded to very low, due to the lack of precision around the confidence interval. The study,
conducted by Philip et al. (2009), began with a very low GRADE, and while there were deductions for directness and precision, the study was already at the lowest level of evidence. On combination of the studies, the final GRADE for the outcome of suicidal ideation was again very low.

The last outcome included in the GRADE analysis was depression, and was it addressed by Gunnell et al. (2009), Rigotti et al. (2010), and Philip et al. (2009). The Gunnell et al. (2009) study GRADE did not change, and its final GRADE level was low. The Rigotti et al. (2010) study started at a high level of evidence, but again due to the lack of disclosure on how depression was determined within the study, the study was lowered one level to a moderate GRADE. The last study included by Philip et al. (2009) started at the very low GRADE level. The study would have been lower further in the study quality category since there was no blinding, no placebo use, and very few participants. Although the study had an increase in one GRADE level due to the large magnitude of effect, as over 75% of the participants had decreased depression symptoms, the final GRADE remained at the very low level. Therefore the overall GRADE for the depression outcome was low.

Based on the studies reviewed, the correlation of varenicline use and suicide appears minimal. But, due to the limitations of the studies and the overall low GRADE based on the analysis, further studies would likely change this conclusion (Guyatt et al., 2008). Currently, there is insufficient evidence to make a definitive decision regarding the safety of the drug, but the studies indicate a weak correlation. That said, varenicline proves to be the most effective form of
smoking cessation available to date. Evidence shows that use of varenicline does cause some adverse events including nausea, vomiting, and sleep disturbances, so providers need to be aware and warn patients of these possible side effects. And while there may be a minimally increased risk of suicide with its usage, the risk of eventually dying from smoking related illness for smokers is 50%. Therefore, when balancing these risks, there is a greater risk of dying from a smoking related illness with continued smoking compared to the unreliable risk of suicidal problems from using varenicline. Hence, the risks of using varenicline for cessation outweigh the risks of continuing to smoke. There needs to be further studies conducted on patients who are at an increased risk of suicide, mainly those with depression and/or other psychiatric illnesses, to see if the use of the drug is safe in these populations. Until research has been done, providers should continue to prescribe its use in these populations with caution. But for the general public, it appears to be a safe and effective means of smoking cessation.
REFERENCES


## APPENDIX

### GRADE Table – Table 1

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Comparison</th>
<th>Quantity and type of evidence</th>
<th>Total number of Participants</th>
<th>Findings</th>
<th>Starting Grade</th>
<th>Consistency</th>
<th>Directness</th>
<th>Precision</th>
<th>Publication Bias</th>
<th>Large Magnitude</th>
<th>Dose-Response</th>
<th>Confounders</th>
<th>GRADE of Evidence for Outcome</th>
<th>Overall GRADE of Evidence Base</th>
<th>Overall GRADE of Evidence Base</th>
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<tbody>
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<td>Varenicline vs NRT</td>
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</tr>
<tr>
<td></td>
<td>Varenicline vs Placebo</td>
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